DARPA'S BIO-REVOLUTION

An Array of Programs Aims to Improve the Safety, Health, and Well-being of the Military and Civilians Alike

By Jonathan Beard

DARPA is hard at work spearheading a "Bio-Revolution." This broad-spectrum strategic thrust develops and leverages advances in all areas of biological and medical sciences to improve Department of Defense (DoD) capabilities. DARPA's Bio-Revolution programs are focused on four thrust areas: Protecting Human Assets, Maintaining Human Combat Performance, Biology to Enhance Military Systems, and Restoring Combat Capabilities after Severe Injury. All of DARPA's Bio-Revolution programs have one mission in mind: to use the life sciences to benefit the U.S. military and save American lives.

DARPA's interest in biological and medical sciences is a relatively recent one, dating back to the mid-to-late 1990s. At that time it became clear to the DoD that the biological sciences, especially biological weapons, represented a low technical hurdle for our adversaries. Developing a biological weapon would not take a huge amount of money or require a large industrialized infrastructure, and the United States recognized that this could make biological weapons the weapons of choice for what was then known as the transnational threat (what we now know as terrorists). DARPA started its biological warfare defense program in order to avoid this technological surprise.

The Protecting Human Assets thrust area will revolutionize biological warfare defense and combat-casualty care. Warfighters are often deployed to rugged, primitive environments and are therefore at risk for contracting dangerous infectious diseases. The threat of intentional attack with biological warfare agents only heightens risk of infection. The DARPA program is developing technologies that will be able to predict and detect threats, and, more importantly, develop highly effective vaccines and therapeutics to any threats within a tactically relevant time frame. And for wounded soldiers, DARPA is developing technologies that will radically transform battlefield medical care, including such ideas as mobile trauma care through telerobotic and robotic medical systems, new therapeutics for pain control, and new ways to generate and store blood products.

Programs in the area of Maintaining Human Combat Performance are aimed at maintaining the warfighter's peak physical and cognitive performance once deployed, despite extreme battlefield stresses such as heat and altitude, prolonged physical exertion, and sleep deprivation.

Warfighters seldom deploy to ideal climates. The effects of desert heat or mountain cold sap physical performance and can lead to serious medical problems. DARPA has developed new technologies to maintain normal body temperature by utilizing the unique heat transfer properties of blood vessels in the palms of the hands and soles of the feet. Other DARPA efforts have addressed the cognitive deficits experienced during sleep deprivation by developing safe approaches that affect only the biological deficits incurred without stimulating the rest of the body. Still other efforts have developed, and now deployed, safe and natural nutraceuticals that not only maintain performance during exertion, but also maintain immune function even after extreme physical stress.

Some of DARPA's programs are biologically inspired. The PowerSwim program, for instance, has developed a human-powered swimming device for combat and reconnaissance swimmers that is based on the swimming approach of many fish and aquatic birds.

Image courtesy of DARPA

In the Biology to Enhance Military Systems area, DARPA is developing materials and devices inspired by living systems, and using these new technologies to create new military systems. "We want to let nature be our guide to better engineering," says Dr. Brett Giroir, director of DARPA's Defense Sciences Office. Activities in this research area include legged robots that perform better than wheeled vehicles in difficult terrain, and new optics that mimic the properties of eyes. The PowerSwim program has developed a highly efficient, human-powered swimming device for use by combat and reconnaissance swimmers. The device uses the same approach to swimming that is exhibited by many fish and aquatic birds, enabling increased swimming speeds at reduced metabolic expenditure.

In the effort to restore combat capabilities after severe injury, DARPA is funding research to understand and harness the natural processes for healing after severe injuries. DARPA's goal in the Restorative Injury Repair program is to find a way to truly heal deep wounds. "We want to shift the typical wound-healing response from one of scar formation and potential loss of function to one that functionally and structurally restores tissue lost to injury," says Program Manager Dr. Jon Mogford. "If we can heal wounds that involve multiple tissue types, regardless of the location of the wound or the tissues involved, we can give injured warfighters back full function and an improved outward appearance."

DARPA's most prominent activity in the Restoring Combat Capabilities after Severe Injury thrust area are the Revolutionizing Prosthetics programs, which are developing a neurally controlled arm and hand prosthesis that will restore full motor and sensory capability to upper extremity amputee patients. This revolutionary prosthesis will be controlled, feel, look, and perform like the native limb.

DARPA is well on its way to creating a Bio-Revolution. In fact, the Fundamental Laws of Biology (FunBio) program has undertaken what is considered by some as the ultimate intellectual challenge. Just as Isaac Newton discovered the laws of physics, the FunBio program is seeking to discover the laws of biology. In the short term, this program is envisioning results that will help warfighters. In the long term, it will dramatically alter the way we think about biology – transforming biology from a descriptive to a highly predictive science enabling new discoveries that will dramatically improve the capabilities of warfighters and the medical personnel that treat them.

OVERVIEW OF DARPA'S
BIOLOGICAL WARFARE DEFENSE PROGRAMS

By Jonathan Beard

A clear and growing national security need is to protect U.S. military forces from biological warfare attacks and naturally emerging infectious diseases. In 1996, DARPA was authorized to conduct an independent program within the DoD to develop technologies to protect U.S. forces against biological attack. At that time, there was little government investment into this emerging threat, and DARPA was called upon to serve its traditional role of anticipating and preventing surprise. As a result, DARPA initiated a broadly focused effort, spanning the spectrum of potential biological warfare defense research. Included in this effort are methods to sense an attack, diagnostics, therapeutics, and vaccines to protect those potentially infected. Also included is consequence management, as well as decontamination of personnel and critical infrastructure.

In 2000, DARPA initiated research into the first potential gaseous decontamination technology, chlorine dioxide, leading to the first proof that, under specific conditions, this gas would kill anthrax spores and sterilize the environment. When the anthrax letter attacks of September 2001 created an urgent need for an advanced building decontamination technology, the DARPA technology was selected by the Environmental Protection Agency as the decontamination technology for the Hart Senate Office building, enabling complete building sterilization and reoccupancy.

Fortunately, DARPA had also funded research to change the paradigm of environmental and personal threat detection. DARPA boldly asserted that a highly technical assay technology called PCR – polymerase chain reaction – could be drastically altered from a sophisticated laboratory technology requiring days of dedicated time of highly trained technicians, to a "point-of-need" test that could be conducted in minutes by any "sergeant" on the battlefield. This technology was also ready after the attacks, and was implemented throughout the country to screen mail for contaminated letters at regional post offices. Millions of tests are now conducted every year, right at the point of need.

One result of the DARPA-funded research is the Handheld Isothermal Silver Standard Sensor, which provides laboratory-quality detection of the full biological threat spectrum (bacteria, viruses, and toxins). The false-alarm rate of this new sensor is significantly better than that of the current "silver standard" laboratory assays.

DARPA also explored optical approaches to biological warfare-agent sensing. Using DARPA-developed wide bandgap materials for optical emission in the ultraviolet region has led to sensors that have reduced power requirements and that are significantly smaller than previously possible. The Department of Homeland Security is using the technology in its Low-Cost Biological Agent Detection System.

To complement these tactical sensors, DARPA developed a "gold standard" sensor/detector for deployment as a strategic national asset to detect any type of pathogen – even unknown and engineered ones – through an innovative method of measuring and weighing nucleic acid sequences. The Triangulation Identification for Genetic Evaluation of Risk (TIGER) sensor has been rigorously validated for biodefense applications, including surveillance for biological warfare agents in environmental samples and analysis of a broad range of biological samples for important human pathogens. DARPA's TIGER effort is completed and the technology has been deployed to a number of places, including the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, Md.; the National Institute for Allergies and Infectious Disease in Bethesda, Md.; and the Centers for Disease Control in Atlanta, Ga.

In addition to specific sensors, DARPA has also developed technologies for a so-called "Immune Building." A building fully equipped with these technologies can sense a chemical or biological warfare attack, and then automatically modifies its heating, ventilation, and air conditioning system to protect the building's occupants. DARPA's

Building Protection Toolkit assists in designing these next-generation building protection systems.

In addition to work in sensors and detectors, DARPA is also focusing on medical therapeutics to treat those exposed during attacks. DARPA reframed the traditional strategy for biological warfare defense by pursuing extremely broad-spectrum therapeutics that could treat many pathogens, including unknown or engineered ones. This contrasts with the less-feasible strategy of stockpiling one drug for each of the thousands of "bugs" out there. Some key research activities include:

CpG. CpG is a broad-spectrum immune enhancer that stimulates the immune system and makes vaccines more effective. This technology is now in late advanced clinical trials for biodefense vaccines, and is also in development for vaccines against cancer and hepatitis.

Universal Antibiotic Target for Ciprofloxacin-resistant Bacteria. Ciprofloxacin is currently our antibiotic of final resort, and is particularly useful against anthrax. DARPA sponsored research that found a target for which new antibiotics can be developed that would handle any natural or engineered ciprofloxacin-resistant pathogens. Lead therapeutic molecules are now in development.

Small Interfering RNA (siRNA). New classes of RNA have been discovered that can inhibit viruses and other pathogens. DARPA sponsored early proof of principle research that is now transitioned to programs both at the Defense Threat Reduction Agency, as well as the National Institutes of Health. The siRNAs are now in testing against diverse pathogens, from avian influenza to Ebola.

2008: DARPA's Biological Warfare Defense Program

Today, DARPA has iterated its vision for the future of biodefense against intentional or naturally emergent threats. That vision is to develop platform technologies to allow the delivery of millions of doses of a definitive therapeutic within 16 weeks of pathogen discovery. DARPA believes there are technical solutions to enable the discovery, production, and delivery of a definitive therapy against any pathogen (known or previously unknown) within 16 weeks. This contrasts sharply to the current time frame of at least 15 years. According to Giroir, "Having the ability to definitely protect against any threat is the final, true protection against enemy threats, as well as against newly emerging diseases, which have for eons wreaked havoc on hominid populations. DARPA is well on its way to realizing this vision."

A prominent program, now nearing transition into use, is the Rapid Vaccine Assessment program. This program has created a high-fidelity, artificial human immune system (AIS) on a chip. The AIS will eliminate years of preliminary, and often non-predictive, animal testing of vaccines and therapeutics before reaching human trials. Having a high-throughput, in vitro human system will allow screening of vaccine candidates in a real human system, reflective of multiple, human genetic types. "Not only will the AIS select likely winners, but more importantly, it will reject the losers before wasting years of development and risking side effects in human test subjects," Giroir says.

Once a basic vaccine, antibody, or immune enhancer has been identified and has undergone pre-clinical evaluation, the recently begun Accelerated Manufacturing of Pharmaceuticals program is developing ways to manufacture millions of doses in only a few weeks – instead of the years required today – at pennies per dose. "To achieve this goal, we are looking at leveraging the large-scale, mass-production industrial fermentation processes used in enzyme manufacturing, using simple organisms such as bacteria and fungi instead of complex, slow, and expensive systems such as chicken eggs or hamster ovary cells," Giroir says. The DARPA program is also supporting research into other highly novel platforms, such as plant- and mushroom-based systems, leveraging the country's enormous agricultural infrastructure. According to Giroir, "Already, this program has demonstrated efficiencies of protein production one hundredfold greater than current techniques. With the assistance of our government partners in the Department of Health and Human Services, DARPA hopes to establish these new technologies and have them FDA-certified by the end of 2011."

U.S. Army photo by Spc. Stephanie Homan

PROSTHETICS

By Jonathan Beard

Jesse Sullivan, a former high-power lineman, lost both arms in 2001 after being electrocuted on the job. In these two photos, he demonstrates the capabilities of the Proto 1 prosthetic arm system during clinical tests at the Rehabilitation Institute of Chicago.

In 2005, DARPA embarked on a bold initiative with the launch of the Revolutionizing Prosthetics program. The goal of this effort is to deliver a prosthetic arm and hand that will restore an upper extremity amputee to full functional capability.

The foundation for this program began in 2002, when DARPA sponsored seminal research through the Human Assisted Neural Devices (HAND) program, which was the first to demonstrate that the brain's neuronal signals could be captured, decoded, and used to drive a peripheral device. In the HAND program, scientists at Duke University and the University of Pittsburgh demonstrated the capability of primates to operate prosthetic arms for reaching and grasping, using real-time signals extracted and decoded from the motor cortex. These neuroscience and signal-processing discoveries allowed DARPA to move on to an even more ambitious goal – to transform current limb prostheses into biologically integrated, fully functional limb replacements that have normal sensory abilities.

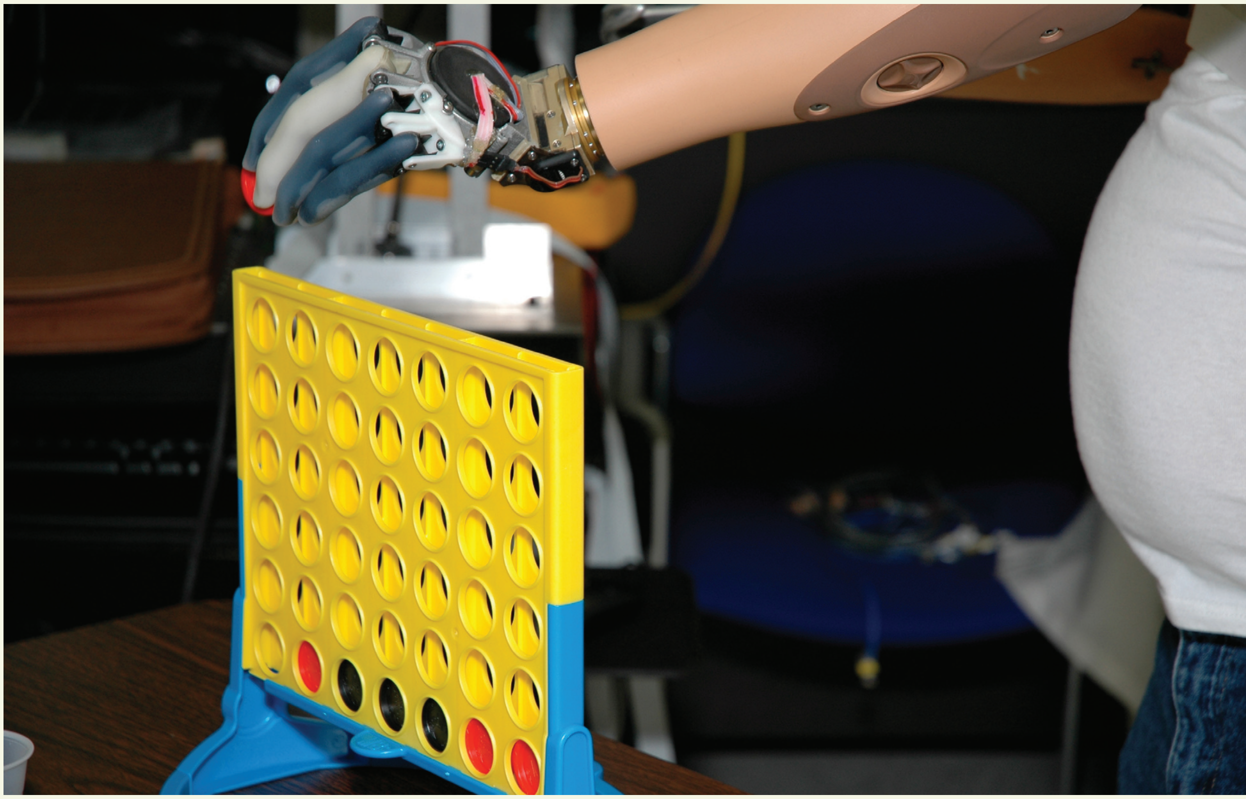
DARPA has two projects – Revolutionizing Prosthetics 2007 and Revolutionizing Prosthetics 2009 – that should deliver prosthetic arms and hands that will make existing models, many of which use technology first invented in the Napoleonic era, look like antiques.

One of the biggest obstacles to overcome is optimally controlling the prosthesis. Presently, protheses are controlled myoelectrically. Residual muscles (myo) are tasked to trigger electrical switches (electric) that control the prosthetic's basic functions. This is not ideal for a variety of reasons. Principally, there are only a limited number of muscles one can use after losing an arm. The hand, for example, has over 20 separate muscles controlling the five fingers, whereas the chest has just one. Thus, because one is limited to just the chest and back muscles after losing an arm, the prosthesis will be limited to just one or two functions, such as opening a hook and bending an elbow. The only problem with this approach is that patients have to retrain their bodies from an intuitive action to a cognitive one. For example, they have to learn to think about contracting a back muscle in order to bend their prosthetic elbow. This unnatural task takes months to learn.

Another limitation is lack of sensation. Today, prosthetics do not return touch, temperature, or pain to the wearer. Importantly, they do not return proprioception, which is joint position sense. Thus, to use the device, the wearer has to look at it.

Modern prosthetics are also ugly. The most functional end terminal device are hooks. They are so unappealing that close to 50

Photos courtesy of the Rehabilitation Institute of Chicago



percent of amputees will not wear them. Instead, they would rather use cosmetic prostheses, which are nonfunctional rubber hands.

To approach this problem, DARPA is taking on two separate but related tasks. Both are monumental in scope. The first is to build a robot arm and hand that has the capacity to do all that a native arm and hand can do. It must have five dexterous fingers, a hand that can conform to perform many tasks, a wrist that can bend and twist, an elbow that can bend and lift weight, and a shoulder that can rotate and reach above one's head and behind one's back. Furthermore, there must be sensors to provide feeling, a power source with a day's worth of duty, a realistic covering that looks like skin and is weatherproof, tear resistant, and will not wrinkle in unusual places. All this has to be packaged into a form that looks like an arm and must weigh no more than 8 pounds, which is what a native arm weighs.

The second task is to develop the means by which the patient's natural intent is used to control the prosthetic. The only means by which this can be accomplished to the high degree of functionality demanded is by using the same approach used to control a native arm, i.e., using the patient's own central nervous system. The previous work done in HAND shows that this is possible. The remaining work is to show exactly how this can be done practically. In addition, sensation must be put back into the patient.

Creating such a revolutionary new prosthetic arm in only four years is something only DARPA can do. "Most Americans who lose limbs lose legs," says Col. Geoff Ling, M.D., who directs the programs. Thousands of people have legs amputated – largely due to peripheral vascular disease resulting from atherosclerosis, diabetes, and other common chronic diseases – which means there is a large market for prosthetic legs. "But this technology does not transfer to prosthetic arms," he explains, "because legs are fairly simple: You walk on them or stand on them." Arms and hands, however, are a different matter: "We use our hands and arms for thousands of different tasks," Ling says, "so that replacing an arm is a very complex problem. What we need is a smart, modular prosthetic arm and hand, one that will have human-like capabilities, look like the native limb, and be controlled directly by the wearer's brain." Ideally, the prosthetic limb generated through DARPA research will not simply enable the user to grasp and manipulate objects, but will provide fine motor control and sensation. Through DARPA research, the prosthetic arm of the future will make a massive leap from a hook and pulley system to an advanced biomimetic device, allowing a user to throw a baseball or feel the grasp of their child's hand.

Ling, who directs both prosthetics programs for DARPA, says that Revolutionizing Prosthetics 2007 has achieved all of its goals. The prosthetics were designed by DEKA Research and Development Corp. of New Hampshire. The team involves both industry and academic partners and is led by Richard Needham. Demonstration of early generation prototypes have used surgical and non-surgical control strategies. DEKA has been able to implement lessons learned from creating devices such as the Segway Scooter

Army Capt. James Watt, an occupational therapist, helps Sr. Airman Dan Acosta through some prosthetic arm warm-up drills on Feb. 23, 2006, in the amputee rehabilitation clinic at Brooke Army Medical Center in San Antonio. Patients at Walter Reed and Brooke Army Medical centers will begin training this year with prosthetics derived from DARPA research.

U.S. Air Force photo/Steve White

and the IBot wheelchair in creating simple-to-operate systems that result in dexterous movement and complex capability.

DARPA's other prosthetic effort, Revolutionizing Prosthetics 2009, is also on schedule. In this case, the major contract was made to the Applied Physics Laboratory (APL) of Johns Hopkins University (JHU), with its team led by Stuart D. Harshberger. In addition to improving on peripheral nerve drive control, the Revolutionizing Prosthetics 2009 prosthesis will have sensors capable of sending signals to the brain, allowing amputees to feel what the prosthesis is grasping or moving. This, if it succeeds, will provide to users much greater control over the hand and arm than existing devices. The goal is to allow the user to individually activate each finger and provide full range of motion and some level of touch-based sensation.

The program has already developed several prototype prosthetics that are currently being tested in clinical trials. These devices are far more advanced than any currently available, enabling many degrees of freedom for complex grasping and individual finger movements, and are designed to be rugged and resilient in all environments.

In January 2007, the first prototype arm was fitted and attached at the Rehabilitation Institute of Chicago, a partner to both the DEKA and JHU-APL teams. Within hours and with minimal training, the user was able to control the arm in all seven degrees of freedom, including a powered shoulder. Today, six patients, including two ex-service members, have accumulated hundreds of hours' experience controlling and using these arms. Control strategies vary from user to user. Some patients implement surgical reinnervation and drive the arms through a series of implanted sensors in their shoulder and pectoral muscles and residual limbs. Others use advanced and intuitive non-surgical methods, allowing the patients to operate a cordless drill or pick up an M&M from a table. One patient has been able to manipulate individual digits of a five-fingered hand using surface electroencephalographic signals, a feat never before accomplished.

This year, patients at Walter Reed and Brooke Army Medical Centers will begin training for this next generation of prosthetics. They will use both prototype limb systems and a Virtual Integration Environment, a simulation environment that will use biologically generated signals to move and manipulate computer models of arms in the clinic as soon as new prototypes are manufactured in the lab. This will allow each user to tailor the responsiveness and control of his prosthetic limb to his needs and daily demands, and will ensure that all patients have access to training with the latest limb systems.

"Eventually," Ling emphasizes, "the brain will be the controller. We're being very aggressive in our approach to this because we know it can be done. This is not a far-off dream; this is tomorrow's technology applied today. We have already had a total revolution in prosthetics in two years, providing our soldiers with the best possible mechanical device that is controlled, in part, by signals from their nervous systems. In two more years, we anticipate having a prosthetic arm that will be controlled by the brain, the way that we control our biological arms."

NEWTON'S LAWS FOR BIOLOGY

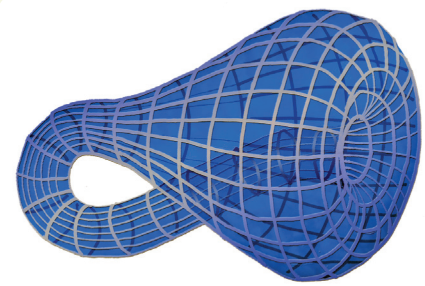
By Jonathan Beard

During the last 50 years, DARPA has established a reputation for investing in projects that provoke major paradigm shifts and forever alter people's ways of thinking. However, it can be argued that perhaps no DARPA project has been as ambitious as the Fundamental Laws of Biology (FunBio) program. It seeks to bring a completely new understanding to biology and, as a result, to provide tangible benefits to the warfighter. Dr. Benjamin Mann, the program manager in the Defense Sciences Office who conceived FunBio, outlines both aspects of the program: "Biology has historically been more descriptive than predictive," he explains. "The subject is believed to be too complicated to explain mathematically and the data sets that biologists amass have been seen as both too large and too messy for mathematicians to work with." Mann hopes that FunBio will bring to biology what mathematics long ago brought to physics: a new, more elegant language with much greater explanatory power.

The initial idea for FunBio came from Dr. Anthony J. Tether, DARPA's director, who challenged his researchers to "find the fundamental laws of biology, much as Isaac Newton and others found the fundamental laws of physics." For Mann, a mathematician, the obvious model for this formidable quest was physics: "There is a clear line of progress," he says, "beginning with Aristarchus of Samos, a Greek astronomer [circa 230 BC], leading to Sir Isaac Newton. Aristarchus was the first person to posit a heliocentric, or sun-centered, universe, an idea that would much later be taken up by Copernicus, Kepler, and Galileo. But it was not until 1687, when Newton published his *Principia*, which included both the equation F=ma and the 'inverse square law,' that science had a suitable mathematical tool to explain the behavior of the planets." Physics, Mann says, has been written almost entirely in mathematics ever since (Einstein's famous $E=mc^2$, for example), and this has endowed it with great precision and power. "Mathematics," Mann concludes, offers "the ultimate intellectual compression."

But what about biology? Traditionally, mathematics has rarely been productively applied to key challenges in biology and medicine. "The problem is that these fields possess many degrees of freedom," Mann says, "and the data sets practitioners collect are large and noisy." What is needed, he says, "is new mathematics that can accurately and reliably explain the intrinsic high-dimensional nature and dynamics of these problems." The new methods must deal with nature's stochasticity, or randomness. Challenges that he can imagine include creating a new mathematical theory to build a functional model of the brain that is biologically and mathematically consistent and predictive, rather than merely biologically inspired.

Although this aspect of FunBio is basic research with almost unlimited goals, one part of the program has already delivered results with enormous potential consequences for both military personnel and the general public. Bacteria that are resistant to antibiotics are an increasing problem everywhere in the world. The rapid spread of resistance to entire families of drugs among unrelated species of bacteria caught medicine by surprise, because one of the mechanisms involved – horizontal gene transfer (HGT) – was neither predicted nor understood by geneticists. What happens is that genes that make bacteria resistant to the penicillin family of antibiotics, for example, have not just been inherited by daughter bacteria – as was expected – but have moved "horizontally" to other species of bacteria in the same environment.



Tools developed by the Topological Data Analysis program at DARPA have been shown to be capable of handling the complexity of massive, multi-dimensional data sets in less time than previously required.

Image courtesy of DARPA

Two FunBio team members, Dr. Michael Deem of Rice University and Dr. Jeong-Man Park of Catholic University of Korea, have developed the first exact solution of a mathematical model of evolution that includes HGT and accounts for this cross-species exchange of genetic material. "Previous calculations," Mann points out, "were limited to models incorporating point mutations – single changes in the DNA sequence." But FunBio researchers have taken powerful techniques from advanced mathematics and quantum physics to incorporate more complex mechanisms of evolution in both bacteria and viruses. One of Deem and Park's predictions is that the speed of evolution has increased over time because bacteria and viruses are exchanging pieces of DNA rather than relying on single random point mutations.

An important tool in the mathematical search for biology's fundamental laws springs from another of Mann's programs, Topological Data Analysis (TDA). The TDA program is developing new mathematical methods and techniques to study massive, multi-dimensional data sets. TDA tools search for the hidden, highly nonlinear, geometric structures and properties of these complicated data sets, helping researchers see characteristics of their data that would otherwise be extremely hard to find. TDA tools have been tested on medical and biological data sets, and have shown that they can handle the complexity of these data sets in a fraction of the time previously required. In one such test, TDA tools were applied to cancer data, and were able to infer disease progression from gene expression data, as well as differentiate between clinical characteristics. One such characteristic was a distinction in tumor type that corresponded to very different survival rates. It is hoped that these technologies will unearth characteristics in biological data sets that will help in the quest for the fundamental laws of biology.